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Mir-21 is a potential therapeutic target in glioblastoma multiforme

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MicroRNAs (miRNAs) are a class of RNAs that regulate gene expression posttranscriptionally. They were originally identified as playing important roles during development in worms, flies, and plants, but their role in a wide range of human cancers has increasingly come under intense scrutiny. Currently, human miRNAs number in the hundreds. They function by binding the 3' untranslated region of target mRNAs, resulting in translational repression or mRNA degradation. Because each miRNA is in the range of 22 nucleotides in length, they can theoretically regulate/target a large number of mRNAs. Distinct miRNAs have been shown to function as either tumor suppressors or oncogenes.

Glioblastoma multiforme (GBM) is one of the deadliest forms of human cancer. Although progress has been made in its treatment, overall prognosis is still poor. To understand whether miRNAs might be involved in the pathogenesis of GBM, Zhou and colleagues performed miRNA expression profiling on a group of GBM cell lines. They found that miR-21 exhibited the greatest increase in expression. Further experiments showed that inhibition of miR-21 by expression of antisense miR-21 (As-miR-21) inhibited proliferation and induced apoptosis both

in vitro and in an *in vivo* xenograft model. Furthermore, the antiproliferative and proapoptotic effects of As-miR-21 were independent of PTEN, which is frequently lost in GBM. These results suggest that targeting miR-21 by either antisense methods or small-molecule inhibitors could be used in the treatment of GBM, regardless of PTEN mutation status.

Runx2 regulates prostate cancer cell survival

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Prostate cancer cells are notoriously difficult to treat, at least in part because of their resistance to cell death. Survivin, a member of the inhibition of apoptosis family of proteins, inhibits activation of caspases, thereby inhibiting apoptosis. Interestingly, it is expressed only in embryonic tissues and in many cancers, not in terminally differentiated tissues. This has made survivin a prime target for cancer therapy. Previous work has shown that bone morphogenetic protein 7 (BMP7) plays a key role in mediating apoptosis in prostate cancer cells. More recently, the antiapoptotic effect of BMP7 in prostate cancer cells has been shown to be mediated through survivin.

When examining the survivin promoter, Lim and colleagues noticed that there were several binding sites for Runx proteins and Smad proteins. Knowing that Runx2, a "master" transcription factor important in mesenchymal differentiation, interacts with Smad proteins, the authors sought to determine whether Runx2 could regulate survivin expression in response to BMP7. They found that Runx2 bound to the survivin promoter *in vivo* and controlled expression of survivin in prostate cancer cells. Furthermore, they established that BMP7 regulated Runx2 expression. To further support a role for survivin in the pathogenesis of prostate cancer, they established that survivin expression increased over time in a mouse prostate cancer model and showed that survivin and Runx2 are expressed in human prostate cancer tissues. It remains to be seen whether this survivin expression pathway is conserved in other cancers known to be dependent on survivin for evasion of apoptosis.

Liver damage is reversible in a NASH model

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Nonalcoholic fatty liver disease (NAFLD) due to obesity and type 2 diabetes has reached near-epidemic proportions throughout the world. NAFLD can lead

to nonalcoholic steatohepatitis (NASH), which is characterized by inflammation, fibrosis, and eventually cirrhosis. Methionine and choline are essential precursors of hepatic phosphatidylcholine (PC) synthesis. Deprivation of methionine and choline leads to decreased PC synthesis, resulting in inhibition of very-low-density lipoprotein assembly, which in turn results in inhibition of triglyceride secretion from hepatocytes. To further understand NAFLD-induced NASH, Mu and colleagues utilized an NAFLD rat model in which rats are fed a methionine- and choline-deficient (MCD) diet. They asked whether endoplasmic reticulum (ER) stress is involved in the pathogenesis of NAFLD-induced NASH and whether the hepatic fibrosis that develops in this model is reversible. Interestingly, ER stress appears to play a prominent role in the establishment of NAFLD. This is not surprising because the ER stress response appears to be an important cellular defense mechanism for a litany of cellular stressors.

The authors also report that they were able to reverse NASH-associated fibrosis by switching rats from an MCD diet to one containing methionine and choline. While these results are encouraging, further work needs to be done to extend them to other model systems and eventually to humans with NASH.

How rheumatoid arthritis spreads to unaffected joints Rheumatoid arthritis (RA) is a debilitating chronic inflammatory disease that initially affects single joints but eventually progresses to involve nearly all joints. One of the most perplexing questions concerning RA is how the disease spreads. As reported in a recent article in *Nature Medicine*, Lefèvre and colleagues employed a clever mouse model of RA to determine the mechanism of spread. In their model, they implanted cartilage-containing RA synovial fibroblasts (RASFs) from RA joints under the skin of severe combined immunodeficient (SCID) mice in order to determine whether they could spread to uninvolved cartilage implanted under the skin of the contralateral flank. They found that RASFs were able to access the blood and migrate to the contralateral flank, invade the uninvolved cartilage, and cause destruction, thus implicating RASFs as important players in the spread of RA.

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Deep exome sequencing identifies genetic basis of rare genetic disorder

The identification of genes responsible for rare monogenic diseases has provided considerable information about disease mechanisms, biological path-

ways, and therapeutic targets. However, identification of the genes involved in these diseases by traditional positional cloning strategies has been hampered by tiny cohorts and other factors. With the advent of massively parallel DNA sequencing technologies that allow whole-genome sequencing of individual patients, strategies for the identification of genes involved in rare genetic diseases have changed dramatically. In a recent article in *Nature Genetics*, Ng and colleagues describe their use of deep exome (exon-only) sequencing to identify *DHODH*, which encodes a key enzyme in the pyrimidine *de novo* biosynthesis pathway, as the gene responsible for Miller syndrome, a rare mendelian disorder. This strategy, in either its present or a modified form, will surely be used to identify a slew of similarly rare genetic diseases of unknown cause.

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TAp63 is a tumor suppressor p63 encodes six different proteins, which has made assessment of its role in cancer challenging. The TAp63 isoforms contain an amino-terminal p53-like transactivation domain and are known to induce apoptosis and inhibit cell-cycle progression. Guo and colleagues report in a recent letter in *Nature Cell Biology* that they directly tested whether TAp63 isoforms could suppress tumorigenesis. Their results showed that TAp63 isoforms were potent tumor suppressors *in vitro* and in an *in vivo* mouse model that developed an increased incidence of sarcomas. Interestingly, the tumor-suppressive functions of TAp63 were dependent on p21^{Waf/Cip1} and Rb but were independent of p53, p19^{Arf}, and p16^{Ink4a}. Furthermore, TAp63 could induce senescence in already established tumors, whether or not p53 was intact. These results suggest that induction of TAp63 could be useful as an anticancer therapy, even in tumors that have lost p53.

Nature Cell Biology 2009;11:1451–1457; doi:10.1038/ncb1988

Minimizing endoplasmic reticulum stress in macrophages as a strategy to reduce atherosclerosis Endoplasmic reticulum (ER) stress has emerged as an important pathophysiological mechanism in a variety of chronic disorders, including atherosclerosis. Macrophages appear to be particularly susceptible to toxic lipids that activate ER stress.

In a study published in *Nature Medicine*, Erbay and colleagues sought to uncover the link between lipotoxic signals, ER stress, and atherosclerosis. They showed that macrophage fatty acid-binding 4 (aP2), a lipid chaperone, integrates the response to toxic lipids, resulting in apoptosis, which contributes to atherosclerotic plaques. Interestingly, inhibition of aP2 reduces atherosclerotic lesions *in vivo*. These results indicate that modulation of the aP2 signaling axis might be therapeutically advantageous in the treatment of atherosclerosis.

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